

cially resistant bacteria that escape the general lytic cleavage that destroys most of their fellows. These withdraw into the tissues, multiply, and then venture again into the circulation. Richardson's work apparently shows that a judicious stimulation of the function of sensitization serves a valuable purpose in preventing these relapses.

In conclusion I wish to say that, so far as I can see today, it is not probable that we will ever get an antitoxin for the treatment of typhoid fever comparable with that which we have for diphtheria, but that the residue may be of service, especially in preventing relapses, and if we can find some method of early diagnosis it may prove of value in aborting the disease.

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**OBSERVATIONS ON THE HYPODERMIC USE OF QUININE AND  
UREA HYDROCHLORIDE IN THE DIAGNOSIS AND  
TREATMENT OF ACUTE AND CHRONIC  
MALARIAL INFECTIONS,**

AND ON THE RESEMBLANCE TO THE SEXUAL CYCLE OF THE HEM-  
AMBEA MANIFESTED BY THE PERIODS OF FREEDOM FROM  
PAROXYSMS THAT ORDINARILY FOLLOW A SINGLE IN-  
JECTION OF ABOUT ONE GRAM OF THIS SALT.<sup>1</sup>

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THE object of this paper is to recall attention to four points in connection with the hypodermic use of quinine and urea hydrochloride in acute and chronic malarial infections: (1) The superiority of this salt over other preparations of quinine. (2) The periods of either six and one-half days approximately, or thirteen days approximately, during which patients previously exhibiting irregular recurrences of paroxysms, or regular quotidian, tertian, or quartan recurrences, remain free from paroxysms following a single injection of about 1 gram (15 grains) of this salt. (3) The similarity between these periods of six and one-half and thirteen days respectively, and the periods of cyst formation and of sporozoite development in the sexual cycle of the parasite, as observed in the mosquito. (4) The diagnostic value of such injections, both in proving and in disproving malarial infection in cases in which parasites have not been discovered in the peripheral blood.

<sup>1</sup> Read by title at the fifth annual meeting of the American Society of Tropical Medicine, Baltimore, March 28, 1908.

A fifth point may be emphasized in passing, as a variant of the first, namely, the probable therapeutic superiority of this quinine salt in pernicious malaria.

In connection with the similarity between the significant periods of the sporogony of the hemamœba and the week and two-weeks freedom periods following the use of quinine in this active form, I have sought, and had search made, for gametes and sporozoites, but without success. I am extremely desirous that the observations should be repeated by observers more skilled in technique and in parasitology, than I and having more continuous control of abundant material.

My experience with the use of the double hydrochloride of quinine and urea in the treatment of malarial infections dates from 1884, when I was chief of clinic in the Medical Out-patient Department of the Jefferson Medical College Hospital, in the service of Professor Roberts Bartholow, whose praise of this preparation led me to its use. Its advantage is extreme solubility, as it dissolves in its own weight of water, thus making possible the administration of a sufficient dose, which is quickly absorbed. Its disadvantage is the liability to produce slough or abscess if one is not careful in the use of the preparation. With due care to make the injection deeply under the skin, but not necessarily into the muscle, and to empty the syringe before withdrawing the needle, so that no drop of the solution shall fall upon the integument as the needle leaves the tissues, such accident need not be feared. An additional precaution invariably employed in my service is to seal the point of puncture with iodoform collodion or with tincture of iodine.

In G. E. deSchweinitz's experiments<sup>2</sup> upon quinine amblyopia, he found the quinine and urea salt much more toxic than any of the other preparations which he employed. Incidentally to the therapeutic studies summarized in the following pages, observations have from time to time been made as to the effect of the drug upon leukocytosis. So far as the gross leukocyte count is concerned, it frequently seemed to reduce the number slightly, but this effect was not invariable, nor did the decrease persist for more than forty-eight hours after the injection. Not rarely, the fall would be followed by an increase above the previous figure. As to differential counts, the observations are insufficient and inconclusive.

**ACUTE MALARIAL INFECTION.**—The observations which here are summarized have been carried out in private practice, at the Jefferson Medical College Hospital, both in the Out-patient Dispensary and in the wards, and at the Philadelphia Hospital. Unfortunately, some of the records have been mislaid, so that accurate statistics cannot be given. Approximately, there have been treated by this

<sup>2</sup> Personal communication; also G. E. de Schweinitz, *Toxic Amblyopias*, Philadelphia, 1896, p. 193

method about 250 cases of acute malarial infection, of which 1 was of quartan periodicity, upward of 100 of quotidian periodicity, and upward of 140 of tertian periodicity, the remaining 5 or 6 exhibiting irregular recurrence. In the 1 case recorded as of quartan periodicity the parasite was identified as the quartan parasite (*Hæmamoeba malarie*). In the others the tertian parasite, of the ordinary (*Hæmamoeba vivax*) or estivo-autumnal (*Hæmamoeba falciparum*) type was, in general, recognized. Unfortunately, the records, while noting the presence or absence of organisms, fail to specify in a sufficient number of cases the exact variety found. It is possible that in some cases quotidian parasites were present and not identified.

In all cases of which note was made, with the exception of 4 instances in which two injections were necessary to bring about the freedom period, there occurred, following a single injection of 1 gram of the quinine and urea salt, especially if this were administered during the paroxysm or within four hours thereafter, a prolonged, definite period of freedom from paroxysms. In about one-third of the cases this lasted between six and seven days, varying from one hundred and forty-one to one hundred and sixty-two hours; in the remaining two-thirds of the cases, the period of freedom was between twelve and fourteen days, varying from two hundred and ninety to three hundred and twenty-five hours. In some of the case-notes these periods are estimated from the beginning of chill to the beginning of chill, and in some cases from the hour of maximum temperature to the hour of maximum temperature. In future observations a uniform method should be followed. It is also quite possible that nurses on duty do not always catch the exact beginning of a chill, or the exact point of maximum temperature. I am inclined to believe that a fair statement of the average freedom periods would be six and one-half and thirteen days respectively; or perhaps it might be stated as seven and fourteen (week and fortnight) *organism days* of about twenty-one to twenty-two hours each. The most frequent figures to be found in the notes concerning the week-cycle are one hundred and forty-seven, one hundred and fifty, and one hundred and fifty-six hours; in the notes concerning the fortnight cycle, three hundred, three hundred and six, and three hundred and twelve hours. As a rule, but not invariably, the cases showing the shorter period of freedom were quotidian in type. Of those exhibiting the larger period, the preponderating number were tertian. The quartan case showed a freedom period of twelve and three-eighths days, with certain peculiarities, a summary of which is given later.

When the injection is made within less than two hours before the time of an expected paroxysm, it usually does not prevent the occurrence of the chill, although the phenomena are, in general, milder than usual. The paroxysm due to follow will, however,

be missed, and the freedom period thereafter be manifested. When the injection is given three or four hours before the time at which a paroxysm is anticipated, it usually prevents the attack. When given between four and eight hours in advance of the expected chill time, the injection will usually prevent both the paroxysm about to be due and its anticipated successor, but sometimes only the latter. The effect cannot be predicted with certainty.

Usually the paroxysms, if tertian, would, after the thirteenth day, resume their former periodicity; or, if quotidian, would, after six and one-half or thirteen days, change to tertian. Rarely did the paroxysms resume the quotidian periodicity. A case of irregular periodicity would assume the tertian, less frequently the quotidian, type. In one instance there is a note made that the paroxysms changed from quotidian to quartan, but as the detailed records are missing and the case dates back to 1885, at which time the specific quartan parasite would not have been recognized, no stress is laid upon this fact.

In other cases, of which 6 are noted (probably all that were observed), after the six and one-half days or thirteen days of freedom, a further freedom period of six and one-half or thirteen days was manifested without further medication; that is to say, the periodicity apparently changed from quotidian or tertian, as the case might be, to what were formerly termed, respectively, the weekly and the fortnightly types. The number of possible observations of this kind was limited, for obvious reasons.

After the occurrence of the freedom period had been demonstrated, and the periodicity of the renewed paroxysms determined, injections were, as a rule, resumed and continued daily in quotidian cases, and on alternate days in tertian cases, until the recovery of the patient was assured; or the drug was administered by the mouth—in capsule—in two doses of 10 or 12 grains (0.75 gram) each, four hours and eight hours, respectively, before the anticipated chill time; or 10 grains (0.65 gram) were given at night and the same quantity in the morning, without special reference to the chill period; or one dose of 20 to 23 grains (1.3 to 1.5 grams) was given between eight hours and four hours before the anticipated chill. On the whole, one method answered as well as another.

When two weeks had passed without paroxysms, the patient was usually dismissed from the hospital, with the injunction to take 20 grains of the drug weekly, in two doses, one of 10 grains on the evening of the sixth day, and one of 10 grains on the morning of the seventh day, calculating from the date of the last paroxysm; and to continue this treatment for at least three months, returning to the hospital or reporting to the Out-patient Department from time to time, for observation.

The case of H. J., observed in October and November of 1907, may be related as a typical instance, illustrating several of the phenomena summarily described (Chart I).

This man had a quotidian intermittent fever, with paroxysms recurring in alternate periods of twenty-one and twenty-four hours. He exhibited the ordinary tertian parasite, and was evidently infected with two broods, maturing at forty-five hours. An injection was given fifty minutes before a paroxysm expected at 11 A.M., on October 26. The chill occurred on time, but its duration was much shortened. The temperature, which in previous attacks had risen to 104° or 105° F., reached only 103°, and fell to the minimum point, 97°, five hours after its maximum had been reached, the fall in previous paroxysms having occupied eight hours. There was no chill on the following day, and the temperature remained practically normal, oscillating between 97° and 98.4° until one hundred and forty-seven hours after the chill, or one hundred and forty-two hours after the temperature had fallen to its minimum. On November 1, the sixth day after the last preceding paroxysm, or the seventh day, including the day of that paroxysm, the temperature rose at 2 P.M. to 102°, remaining elevated for three hours, and reaching normal at 8 P.M., but there was no chill; the paroxysm was incomplete. On November 3, at 9.45 A.M., about forty-three and one-half hours after this incomplete paroxysm, a chill began, and the maximum temperature point of this attack, 104°, was reached at 11 A.M.; that is, about forty-five hours after the maximum point of the paroxysm without chill that had preceded it. The temperature reached its minimum at 8 P.M. A chill occurred at 7.15 A.M. on the fifth of November, again about forty-five and one-half hours after the previous chill, maximum temperature being reached at 8.45 A.M., and minimum temperature not until 2 A.M. the following day. The next chill occurred on the 7th of November at 7.45 A.M., forty-eight and one-half hours after the previous one, maximum temperature occurring at 11 A.M. and minimum temperature at 11 P.M. The fall of temperature was possibly hastened by the second injection of quinine and urea hydrochloride, which was given during the declining stage of this paroxysm, at 2 P.M. No further paroxysm was permitted to occur. The treatment was continued by injections on alternate days until November 16, and the patient left the hospital, apparently well, on November 18.

Examination of the blood had shown the presence of parasites in various stages; hyaline, pre-segmenting, segmenting, intracellular pigmented, and extracellular pigmented forms being present, all in large numbers.

October 24. 200 fields were counted and 600 parasites found.

October 25. A similar count was made.

October 26. 200 fields were counted; 560 parasites were found.

On this day an injection was given.

October 27. 200 fields were examined; 12 parasites were found—8 intracellular pigmented and 4 extracellular.

October 29. 200 fields were examined; 3 parasites were found—2 intracellular pigmented and 1 extracellular.

October 30. 500 fields were examined; no organisms were found.

October 31. 500 fields were examined; no organisms were found.  
November 1 (the sixth day after the injection). 200 fields were examined; 34 parasites were found—young hyaline, 31; mature intracellular, 2; extracellular pigmented, 1. It was on this date that the temperature reached  $102^{\circ}$  at 2 P.M.

November 2. 200 fields were examined; 90 parasites were found—hyalin, 8; intracellular pigmented, 60; pre-segmenting, 22; segmenting parasites were specially looked for, but none found.

November 3. 200 fields were examined; 49 parasites were found—hyaline, 22; intracellular pigmented, 10; pre-segmenting, 16; segmenting, 1. On this day the chill occurred, with a temperature of  $104^{\circ}$ .

November 4. 200 fields were examined; 288 parasites were found—hyaline, 20; intracellular pigmented, 264; segmenting, 4. Temperature was  $102^{\circ}$  at the time of observation, but no chill occurred.

November 5 (last chill day). 200 fields were examined; 236 parasites were found—hyaline, 188; intracellular pigmented, 32; segmenting, 16. Injection was given on this day. No further chill occurred, and the number of parasites steadily diminished until finally they disappeared.

The accompanying charts, for which I am indebted to Drs. Robinson and Moore, internes at the Philadelphia Hospital, exhibit the decrease, disappearance, and return of parasites in this case and the temperature curves indicative of periodicity and freedom preceding and following the injection of the drug (Charts I, II, III).

One other case—that of quartan fever, being the only example of its kind in the series—may be cited in brief summary. It shows a period of freedom of twelve days and nine hours, interrupted by abortive disturbances on the intermediate days of paroxysm; and an apparent tendency to alternate periodicities of seventy-eight and eighty-four hours respectively. Whether the twenty-one-hour and forty-two-hour disturbances noted may not have some relation with quotidian and tertian periodicities, and what are the possibilities of a multiple infection, or of changes of type in organisms, are questions suggested by the case, but not answered (Chart IV).

Cosmo di G., aged twenty-three years, a native of Italy, by occupation a laborer, came into the hospital on June 17, 1907, with a history of having had an attack of chills and fever in Italy four years earlier, the paroxysms, according to the patient's statement, recurring after intervals slightly in excess of three days. The duration of this attack was three weeks, and the patient, although he suffered from irregular fever on various occasions thereafter, had had no second attack. The present illness began about five weeks before admission to the hospital, with a violent chill, which lasted about three hours and was followed by fever and sweating. Later, severe muscular pains developed, with extreme tenderness, especially of the trunk and abdomen. This was followed by the appearance of

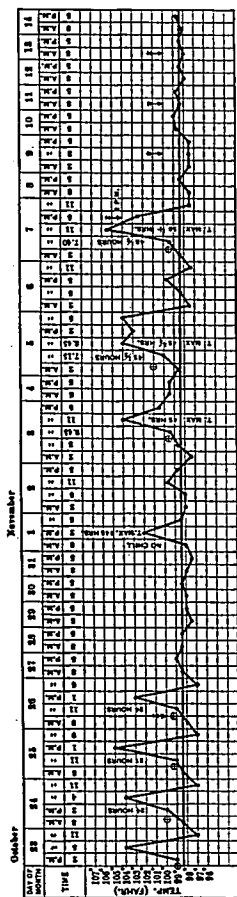


CHART I.—Quotidian intermittent fever. Free period 147 hours. Change of type to tertian. (Henry J.; Autumn, 1907.)  
 • Injection of 1 gram of quinine and urea hydrochloride.  
 • Beginning of chill.

what, from the patient's description, seems to have been a maculopapular eruption, lasting about one day. According to the patient's statement, these paroxysms recurred every third day, and were followed by a like eruption. He had been given some pills, presumably quinine sulphate, but had not recovered.

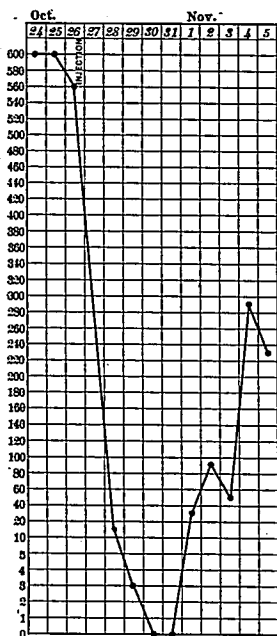


CHART II.—Showing disappearance and reappearance of organisms after the injection of 1 gram of quinine and urea hydrochloride. (Case of H. J.)

Physical examination of the patient upon admission revealed nothing significant, other than slight enlargement and tenderness of the spleen. Irregularly distributed over the trunk and abdomen was a papulo-œdematous eruption, consisting of central spots of a pinkish color, surrounded by a purplish areola. This gradually faded, reappearing with high temperature paroxysms. After treat-

ment was begun it disappeared altogether. The temperature upon admission was  $101.3^{\circ}$  at 5 p.m., June 17. Chart IV shows the course of the temperature during the patient's stay in the ward. Previous to the injection of 1 gram of quinine and urea hydrochloride, three periods of maximum temperature (about  $103^{\circ}$  F.) were noted, the intervals being, respectively, eighty-four hours and seventy-eight hours. Periods of minimum temperature (about  $97^{\circ}$  F.) followed the maximum temperature after intervals of, respectively, twenty-four, thirty-six, and twenty-four hours. Each of the periods

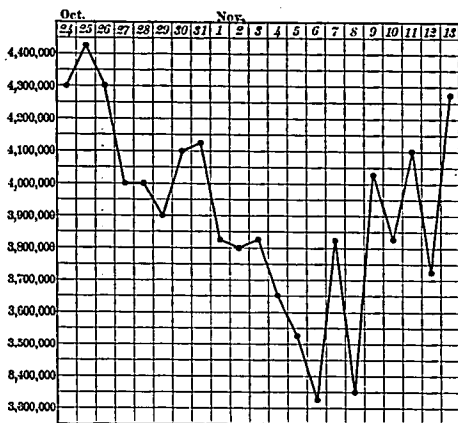


CHART III.—Erythrocyte count diminished after injection of quinine and urea hydrochloride (October 26), until disappearance of recrudescence organisms; then increasing interruptedly. The leukocytes varied during this period from 4600 to 4000, falling to the latter number on October 28, when the temperature became normal following the injection, and the parasites were only 12; they gradually rose, with remissions in count up to 4400 on November 5, when the temperature was  $104.2^{\circ}$ , and the number of parasites was 236. (Case of H. J.)

of maximum temperature was preceded by a chilly sensation and followed by sweating. The decline of temperature to the normal point, or just above, occurred in from three to twelve hours, without medication.

The blood on the day following admission showed: hemoglobin, 100 per cent.; erythrocytes, 5,104,000; leukocytes, 13,800—polymorphonuclear, 73 per cent.; small lymphocytes, 13 per cent.; large lymphocytes, 13 per cent.; eosinophiles, 1 per cent. No organisms were found in several slides prepared from the fresh blood, nor were

they discovered either in stained or unstained specimens until the 26th, when intracorporeal forms were seen. On the 28th, the day on which the paroxysm, if quartan, was again due, both intra-

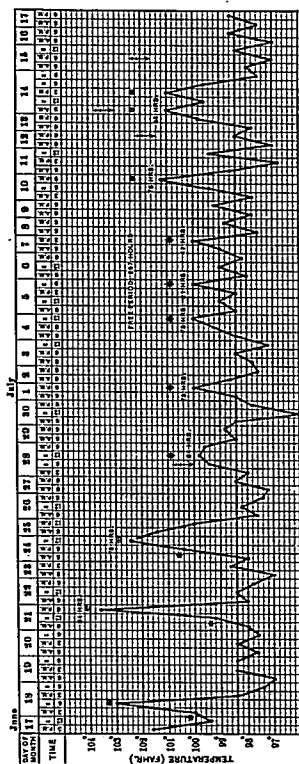


CHART IV.—Quartan Intermittent fever. Free period 297 hours. (Cosmo di G.; Summer, 1907.)  
 \* Beginning of chill.  
 • End of chill.  
 ♦ T. rise without chill.  
 † Injection of 1 gram of quinine and urea hydrochloride.

corporeal and extracorporeal forms were identified as the quartan parasite.

On June 28, at 6 A.M., six hours in advance of the paroxysm anticipated on that day, which was apparently due to occur eighty-four

hours after the preceding paroxysm, the injection was given, the temperature at that time being 99.4°. No chilliness was felt, but the temperature rose 4 points to 99.8° F., about 3° less than the preceding maximum point and 4° less than the paroxysm with which its period of eighty-four hours apparently related it. No further injection being given, a period of temperature rise (100°) manifested seventy-eight hours later, another rise, again after seventy-eight hours, another twenty-one hours later, and another forty-two hours later. The patient complained of nothing. There was neither chilly sensation nor what might be considered marked rise of temperature until July 10, at 9 P.M., seventy-eight hours after the rise of temperature last noted, two hundred and ninety-seven hours (twelve days and nine hours) after the abortive temperature rise following the injection, and three hundred and eighty-one hours after the last preceding definite paroxysm. The next paroxysm, with a temperature rise to 101°, occurred July 14, at 9 A.M., the interval being eighty-four hours. This paroxysm shows a double crest, the second rise occurring six hours later than the first. Following this, injections were given at such intervals as to control the paroxysms and assure recovery from the acute attack. Treatment appropriate to chronic malarial infection was then instituted.

During the period of observation the following notes were made concerning organisms:

- June 26. Malarial organisms found—intracorpuseular forms.
- June 27. Malarial organisms found.
- June 28. Organisms—quartan—found. Injection given.
- June 29. Coarsely granular bodies—intracellular, peripherally located. A few hyaline bodies found.
- June 30. Extracorpuseular and intracorpuseular bodies found. The intracellular bodies were oval in shape.
- July 1. None found.
- July 2. Intracellular bodies, with coarse pigment, sluggishly motile; extracellular pigmented bodies.
- July 3. Same as above, pigment more peripheral.
- July 4. Same as above.
- July 5. Nothing found.
- July 6. Nothing found.
- July 7. Nothing found.
- July 8. Motile bodies (intracellular) found.
- July 9. Motile bodies (intracellular) found.
- July 10. Temperature rise. Intracorpuseular forms and extracellular motile bodies found.
- July 11. Intracorpuseular forms and extracellular motile bodies found.
- July 12. No parasites found.
- July 13. Parasites found, pre-segmenting forms.
- July 14. Paroxysm. Injection given. A few parasites.

July 15. None found.

July 18. None found.

July 30. None found.

Temperature charts are also shown of a number of cases taken at random (Charts V, VI, VII). It will be observed that in one of these quinine chlorhydrosulphate was used instead of the urea salt and was in this instance efficacious. Other observations were made with it. While therapeutically active, it did not prove so uniformly dependable as the urea salt in the matter of the defi-

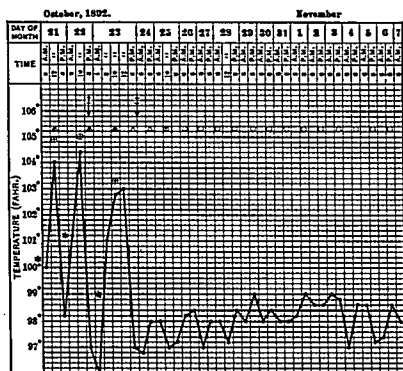


CHART V.—Quotidian intermittent of 30 days' duration prior to treatment. Two injections. Recovery. (John S.; Autumn, 1892.)

\* Beginning of chill.

• End of chill.

† Injection of 1 gram quinine and urea hydrochloride.

▲ Organisms, pigmented, numerous.

△ Organisms, pigmented, few.

● Organisms, hyaline, few.

○ No organisms.

nite freedom period. Drawings of parasites observed were made in 1892, by Dr. Claribel Cone, then interne at the Philadelphia Hospital and now professor of pathology in the Woman's Medical College of Baltimore, to whom I am also indebted for careful notes of the cases which were under her immediate care.

**CHRONIC MALARIAL INFECTIONS.**—In chronic malarial infections of long standing, especially in those cases which exhibit considerable enlargement of the spleen or liver, or both, with or without marked alterations of the blood, quinine alone, even in the form of the combination with urea, has not been sufficient to bring about recovery.

The quinine and urea salt, however, has seemed more efficacious than other preparations of cinchona and its alkaloids; with the exception of cinchonidine salicylate, and in no case has treatment without quinine been so satisfactory as when quinine has been used in con-

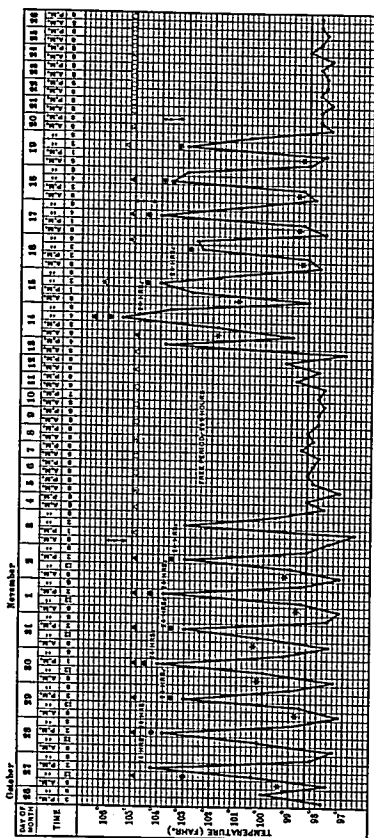


CHART VI.—Quotidian Intermittent. Free period 201 hours. (Jos. D.: Autumn, 1892.)  
 \* Beginning of chill.  
 † Injection of quinine and urea hydrochloride.

Δ Organisms, pigmented, numerous.  
 ○ Organisms, hyaline, few.



junction, at various times, with salicin, methylthionin hydrochloride, arsenic, iodine, iron, and radiotherapy.

In those cases of chronic malaria in which there is a tendency to recurrence of acute exacerbations, whether manifesting as chills and fever or as gastric or nervous disturbances, the quinine and urea hydrochloride has been of distinct advantage in two ways: (1) When the recurrence is periodic, or assumes, after its initiation, a periodic type, quinine and urea hydrochloride used hypodermically or by the mouth, in appropriate dosage, and at a suitable time, will cause the acute symptoms to disappear promptly. For the remedy of the underlying cachexia or chronic affection, other means are additionally necessary.<sup>3</sup> (2) In cases in which the symptoms are irregular the injection of a small dose of quinine and urea hydrochloride will frequently bring about some definite order, either in the quality or time of the symptoms; after which they can be dealt with in the same manner as cases spontaneously definite and periodic. In addition, the diagnosis is frequently made clear by the appearance in the peripheral blood of hemamœbæ, sometimes of atypical character, but still recognizable as varieties of the malarial parasite. This phenomenon will be spoken of more particularly in the next division of the subject, which concerns diagnosis.

DIAGNOSIS.—In two ways has the hypodermic use of the double hydrochloride of quinine and urea proved useful in diagnosis.

1. There are certain cases, evidently of acute infection, which resemble malarial fevers in the character or periodicity of the paroxysms, but in which malarial organisms cannot be found in the blood. There are certain other cases in which, despite the aberrant nature of the paroxysms, there is reason to suspect a malarial origin or complication, and in which, nevertheless, malarial hemamœbæ have not been discovered. In nearly every instance of either of these groups the presence or absence of malarial infection can be predicated upon the patient's reaction to a single injection of the urea and quinine salt. The prolonged freedom period having been found to occur invariably in every case in which the organisms had been demonstrated, it is reasonable to assume that its occurrence indicates the dependence of the symptoms upon undiscovered, perhaps deep-dwelling parasites, and that its absence means the absence of malarial infection.

Thus, in the course of the earlier observations at the Philadelphia Hospital, at a time when 5 cases of intermittent fever of definitely proved malarial origin were under treatment, and manifesting, some the six and one-half days, and others the thirteen days, freedom period, there was a sixth patient who exhibited what appeared to be a typical temperature curve of quotidian intermittent fever, but in

<sup>3</sup> See also the author's articles in "The Polyclinic," Philadelphia, February 15, 1884, and January 15, 1896; and "The Philadelphia Polyclinic," March 15, 1893, and September 3, 1898.

whose blood malarial organisms could not be demonstrated. He received a diagnostic injection of 15 grains of quinine and urea hydrochloride, which induced merely a temporary fall of temperature. Renewed questioning then elicited from the patient what had theretofore been denied, namely, a history of syphilitic infection some six months previously; and recovery promptly followed the use of mercurial inunctions.

In cases of typhoid fever, in which the temperature has tended to assume, at some period of the case, an intermittent type, but in which malarial organisms have not been found in the peripheral blood, diagnostic injections have, in some instances, been followed by the freedom period and in others have not so been followed. In these

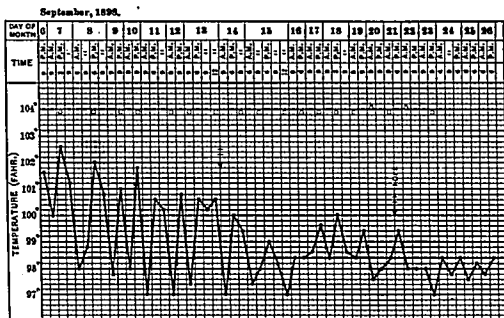


CHART VIII. (Illustrating diagnosis).—Mixed infection; typhoid and malaria. Widal reaction positive. Rose spots. (X. Y. Z.; from Tampa, Fla.)

↓ Quinine and urea hydrochloride injected.

○ No organisms found.

△ Organisms found.

instances, and especially among soldiers of the Cuban war, observed in the months of July, August, and September, 1898 (Chart VIII), it was found that the freedom period usually occurred in patients whose marked loss of hemoglobin would in any event have raised suspicion as to malarial complication, that is to say, of double infection—malaria and typhoid. In some of those in whom the quinine treatment was not continued, because it did not seem to be clinically necessary, the malarial organisms made their appearance during convalescence, after the typhoid infection had run its course. In others, the continuance of the quinine treatment presumably prevented such definite demonstration of the diagnosis. In those cases in which a single injection of the quinine and urea salt had a temporary antipyretic effect, but was not followed by a prolonged freedom

period, malarial organisms did not make their appearance so long as the patients remained under observation; and it is fair to conclude that in these cases that form of infection was absent.

2. The other method in which the injection of the quinine and urea salt has proved useful diagnostically has already been referred to in speaking of the treatment of chronic malarial infection. It was suggested to me by an old observation of Archibald Billings.<sup>4</sup> In cases of doubtful diagnosis the injection of a quantity of the drug not sufficient to secure a definite freedom period will frequently cause the appearance in the peripheral blood of organisms recognizable as normal or atypical forms of the hemamoeba of malaria, and this has been observed so frequently and in so many diverse conditions that I am inclined to look upon its absence after, say, half a dozen injections, varying from three days to a week apart, and in doses increasing from 0.3 to 1 gram, as virtually excluding malarial infection. A typical instance of the value of this use of the quinine and urea salt is the case of chronic malarial infection with splenomegaly and blood changes resembling those of Banti's disease,<sup>5</sup> studied in conjunction with Dr. R. C. Rosenberger and presented to the College of Physicians of Philadelphia, in March, 1904. I am of the opinion that in such cases the organism is resting in some larval form—if the expression be appropriate—probably in the spleen or bone marrow, and that its appearance peripherally is part of a defensive, reproductive reaction to the paratoxic effect of quinine. That organisms do remain latent for long periods is well known; and I have elsewhere referred to a case in which they had reappeared annually for twenty years, provoking, usually, a gastric crisis. This phase of the subject, also, I hope some competent investigator will look into.

<sup>4</sup> A. Billings, *First Principles of Medicine*, London, 1838, p. 218.

<sup>5</sup> *AMER. JOUR. MED. SCI.*, August, 1904; *Trans. Coll. Phys. Phila.*, 1904; *Phila. Hosp. Reports*, 1905.